B

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/624,317	07/22/2003	Nikolay Korokhov	D6471	1681

7590 04/07/2006

Thomas J. Kowalski, Esq.
c/o FROMMER LAWRENC & HAUG LLP
745 Fifth Avenue
New York, NY 10151

EXAMINER	
SCHLAPKOHL, WALTER	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/624,317	KOROKHOV ET AL.	
	Examiner	Art Unit	
	Walter Schlapkohl	1636	uaj

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5 and 7-20* is/are pending in the application.

4a) Of the above claim(s) *4,11,19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,7-10 and 12-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/13/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of the papers filed on 1/9/2006 is acknowledged. Claims 1, 3-5 and 7-20 are pending.

Claims 4, 11 and 19-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 8/1/2005.

This application contains claims 4, 11 and 19-20 drawn to an invention nonelected with traverse in papers filed 8/1/2005. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Information Disclosure Statement

Receipt of the IDS filed on 3/13/2006 is acknowledged.

Claim Objections

Claim 1 is objected to because of the following informalities: claim 1 recites "Staphylococcus A" in line

3. It appears Applicant intended Staphylococcus aureus.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1, and therefore dependent claims 3, 5 and 7-8, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

This is a new rejection necessitated by amendment.

Claim 1 recites "said *modified* fiber protein" in line 7. There is insufficient antecedent basis for this limitation in the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5, 7-10 and 12-18 are rejected under USC 112, first paragraph, because the specification, while being enabling for a recombinant adenovirus (Ad) with (i) a heterologous gene, (ii) a wild type Ad5 fiber protein with the immunoglobulin-binding domain (Cd) of *Staphalococcus aureus*, and (iii) a gene encoding a fusion protein comprising an immunoglobulin Fc domain and a targeting ligand selected from the group consisting of CD40 ligand and a single chain fragment (scFv) of anti-human CD40 antibody, does not reasonably provide enablement for *in vivo* targeting of the vector to a cell that expresses a cell surface molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

This rejection is maintained for reasons of record set forth in the previous Office action.

Claims 1, 3, 5, 7-10 and 12-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This rejection is maintained for reasons of record set forth in the previous Office action.

Response to Arguments

Applicant argues that the amendment of claim 1 to insert the limitations of the presently canceled claims 2 and 6 renders the enablement and written description rejections moot. Applicant further argues that an enabling disclosure is all that is required and Applicant need not have reduced the invention to practice prior to filing. Applicant further argues that the state of the art pertaining to the invention was not unpredictable at the time of filing and thus could have been relied on for guidance in practicing the claimed invention. Applicant further argues that the specification teaches that the virus and the targeting ligand self-associate into a stable complex via a modified fiber protein with the C domain of *Staphylococcus aureus*, proving the feasibility of the formation of targeting vector complexes. Applicant further argues that other targeting ligands have been constructed

such as the recombinant protein comprising the extracellular domain of human CAR as reported by Dmitriev et al and recombinant protein Fc-CD40L as reported by Lo et al. Applicant further argues that Example 7 teaches that all Cd-modified Ad were able to employ the Fc-G28.5 ligand for CD40-mediated infection, with no significant variations between the vectors. Applicant further argues that Examples 8 and 9 teach preparation of complexes of Ad with Fc-containing targeting ligands and that these Examples demonstrate the ability of the complexes to infect CD40-positive cells. Applicant further argues that Example 10 illustrates that *in vitro* transduction of primary human dendritic cells with the CD40-targeted vectors. Finally, Applicant argues that the modifications made to the claims as well as the examples cited in the arguments together serve to obviate the rejections since they clearly convey that the present invention is indeed enabled.

Examiner has considered Applicant's arguments carefully, but has respectfully found them unpersuasive for the following reasons. While Applicant has amended claim 1 to include the limitations of claims 2 and 6, Applicant is respectfully reminded that the rejections of record under 35 U.S.C. § 112 in the previous Office action included

claims 2 and 6. Therefore, the incorporation of those claim limitations into claim 1 is alone not enough to obviate the rejections of record.

Examiner agrees with Applicant that an enabling disclosure is the minimum requirement for enablement and that Applicant need not have a working example in the disclosure in order for Applicant to meet the enablement requirement. However, neither the instant specification alone (including all the Examples cited by Applicant in the arguments), nor the instant specification in view of the amendments to claim 1 and the prior art, are sufficient to enable a targeted recombinant adenovirus vector comprising (i) a gene encoding a heterologous protein; (ii) a wild-type Ad5 fiber protein comprising an immunoglobulin binding domain of *Staphylococcus aureus*; and (iii) a gene encoding a fusion protein comprising a targeting ligand selected from the group consisting of CD40 ligand and a single chain fragment (scFv) of anti-human CD40 antibody and an immunoglobulin Fc domain, wherein binding of said immunoglobulin-binding domain to said Fc domain connects said targeting ligand to said adenovirus, thereby targeting said adenovirus vector to a cell that expresses a cell surface molecule that binds to said targeting ligand.

While the amendments to claim 1 address *some* of the issues raised in the previous Office action with regard to the rejections under 35 U.S.C. § 112, and while Applicant has pointed to relevant portions of the specification that have been considered by Examiner, the amendments still do not address important issues which were raised in the previous rejections made under 35 U.S.C. § 112.

Among the most salient of the issues raised in the earlier Office action which remains unaddressed is the ability of the recombinant adenovirus to target CD40-positive cells *in vivo*. For example, Examiner presumes that Applicant has cited Lo et al (Protein Engineering 11:495-500, 1998; IDS Reference AQ) and noted that the instant specification teaches that the modified adenovirus and the targeting molecule are able to associate with each other in response to Examiner's assertion that the Fc domain-ligand fusion protein must be expressed at amounts abundant enough for complex formation between it and the virus and the targeted cell-surface molecule. Lo et al shows that recombinant fusion proteins can, indeed, be produced in large amounts and the specification shows that, when first purified and then incubated in the presence of the virus, an Fc domain-ligand fusion protein can complex

with the virus *in vitro*. Yet the specification fails to disclose how such a fusion protein would be secreted with the proper timing and abundance so as to allow for an Ad-Fc binding-domain::Fc-ligand::surface molecule complex to form such that specific targeting is able to take place, especially in a complicated *in vivo* context.

This is exacerbated by the fact that the amendment to claim 1, while limiting the fiber protein to a wild-type Ad5 fiber protein comprising an immunoglobulin binding domain of *S. aureus*, still encompasses such a protein wherein *any* Fc-binding domain can be present in any position within the wild-type Ad5 fiber protein. As stated in the previous Office action, Everts et al (Current Gene Therapy 4:337-346, 2004, of record) teach that there is a size limitation with regard to the peptides that can be inserted into the C-terminus of the Ad fiber protein before trimerization is inhibited, wherein, in one case, 27 amino acids was found to be above the limit. Tolerance and function of the inserted immunoglobulin sequence would depend largely upon the insertion point and the size and character of the immunoglobulin domain.

Furthermore, none of the examples cited in Applicant's response address arguments drawn to the ablation of the

natural tropism of the adenovirus to, e.g., the liver, which has been shown to occur with Ad5 - even when the wild-type Ad5 fiber protein has been modified. Therefore, Applicant's arguments are respectfully found unpersuasive.

Request for Interview

Applicant's request for an interview is acknowledged. Applicant may call the Examiner at the number below to set up a time. Examiner's hours have been slightly modified recently and also appear below.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the

THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to the Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is (571) 273-8300. Note: If Applicant does submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent

Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent applications to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at (800) 786-9199.

Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should be directed to Walter Schlapkohl whose

telephone number is (571) 272-4439. The examiner can normally be reached on Monday through Thursday from 8:30 AM to 6:00 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.

Walter A. Schlapkohl, Ph.D.
Patent Examiner
Art Unit 1636

March 29, 2006

NANCY VOGEL
PRIMARY EXAMINER